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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,227	10/03/2003	Hiroaki Ito	053466-0365	8597

22428 7590 07/25/2008

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EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
07/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,227	ITO ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 22-47* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 22-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Original claims 1-19, 22-42 are withdrawn from consideration. Claims 20-21 have been canceled (6/16/08). Amended claim 43 and previously presented claims 44-47 are under consideration by the Examiner.

2. Receipt of applicant's arguments and amendments filed on 6/16/2008 is acknowledged.

3. The following previous objections and rejections are withdrawn in light of applicants amendments filed on 6/16/2008:

(i) the rejection of claims 43-47 under 35 U.S.C. 112, second paragraph; and

(ii) the rejection of claims 43-44 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,888,510 ('510 patent); and

(iii) the rejection claims 43-47 under 35 U.S.C. 103(a) as unpatentable over U.S. Patent No. 5,888,510 ('510 patent) in view in of Queen et al. (U.S. Patent No. 5,530,101).

4. Applicant's arguments filed on 6/16/2008 have been fully considered and were persuasive in part. The issues remaining are restated below.

Claim rejections-35 USC § 112, scope of enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 43-47, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating inflammatory bowel disease by administering an effective amount of monoclonal antibody, PM-1 or MR16-1 against the human IL-6 receptor, does not reasonably provide enablement for a method of treating all inflammatory diseases by administering "all" interleukin-6 receptor antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth at pages 3-7 of the previous Office action (12/5/2006), page 3 of the previous Office action (8/15/07) and pages 2-9 of the previous Office action (1/15/08).

Applicants argue that the specification acknowledges, that the skilled artisan would have only needed to apply routine, commonly known methods to determine applicable IL-6 antagonists and although this process may constitute experimentation, it hardly rises to the level of "undue experimentation" under the enablement requirement. Applicants also argue that consequently, because one skilled in the art would have to perform "undue experimentation" to determine appropriate antibodies in addition to PM-1 and MR16-1, the claims do not lack enablement for all anti-interleukin-6 receptor antibodies which bind to interleukin-6 receptor, block signal transduction by IL-6 and inhibit the biological activity of lL-6, as claimed. Furthermore, Applicants argue that on page 22 of Chuntharapai, the reference teaches that "[o]ne can select antagonistic MAbs to a particular receptor by determining their abilities to inhibit bioactivities of the relevant ligand." This description points to the fact that one skilled in the art would appreciate how to identify appropriate MAbs, based on their bioactivity. However,

contrary to Applicants arguments, the issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990), and In re Wands, 8USPQ2d, 1400 (CAFC 1988). If Applicants will kindly review page 1404 of In re Wands, they will find that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. Applicants arguments that the standard is that of testing appropriate anti-receptor antibodies to determine which antibody has the following properties: binds to interleukin-6 receptor, blocks signal transduction by IL-6 and inhibits the biological activity of IL-6, is a position that has been routinely dismissed by the courts, as shown by the decisions cited above.

The instant claims are not limited to administering naturally-occurring compounds in the claimed method and the instant specification does not provide a description of a repeatable process of producing and administering anti-IL-6 receptor antibodies in the claimed method. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues of the IL-6 receptor which are required for functional and structural

integrity of the protein. It is this additional characterization of the IL-6 receptor protein that is required in order to obtain the functional and structural data needed to permit one to produce an IL-6 receptor antibody which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation. The Chuntharapai reference has been cited for the proposition that antibodies can be agonistic or antagonistic to a particular receptor. However, it is the screening for the desired antibody in light of the working examples and guidance provided by that specification, that is considered undue experimentation. The interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not, without actually making and testing them, then the instant application does not support the breadth of the claims.

Claim rejections-35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6a. Claims 43-44, 47, are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 96/38481.

This rejection is maintained for reasons of record set forth at pages 12-13 of the previous Office action (12/5/2006), pages 4-5 of the previous Office action (8/15/2007) and pages 10-11 of the previous Office action (1/15/08).

Applicants argue that the '481 reference teaches that blocking of all gp 130-related signals is useful for treatment of inflammatory diseases and that the present invention treats inflammatory bowel diseases through blocking only the IL-6 related signal. However, contrary to Applicants arguments, claim 43 recites "comprising administering" which is open language and includes administering antibodies which bind to IL-6 receptor/IL-6 complex which complex binds to gp130, blocks signal transduction by IL-6 and therefore inhibits the biological activity of IL-6. Therefore, the method of treating inflammatory diseases as encompassed by the instant claims, is not specific to blocking a signal only through the IL-6 receptor but also encompasses blocking a signal via the other receptors i.e. leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M and cardiotrophin-1 receptors. Therefore, the instant claims include an antibody that not only blocks IL-6 signal transduction but the signal transduction via the leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M and cardiotrophin-1 receptors. Therefore, the reference anticipates instant claims 43-44, 47.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7a. Claims 43-47 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 96/38481 in view of Queen et al. (U.S. Pat No. 5,530,101).

This rejection is maintained for reasons of record set forth at pages 13-14 of the previous Office action (12/5/2006), pages 5-6 of the previous Office action (8/15/2007) and pages 12-13 of the previous Office action (1/15/08).

Applicants argue that the Queen reference teaches the production of chimeric antibodies and the humanization of monoclonal antibodies as well as designing a humanized antibody that retains affinity for its antigen and that nothing in this reference suggests using an antibody fragment of an anti-interleukin-6 receptor to treat inflammatory bowel disease. Applicants argue that Queen does not describe treating inflammatory bowel disease by *administering an anti-interleukin-6 receptor antibody which binds to interleukin-6 receptor, blocks signal transduction by IL-6 and inhibits the biological activity of IL-6,* as claimed and that Queen does not even mention an IL-6 receptor, much less treating inflammatory bowel disease by administering an antibody to an IL-6 receptor. However, contrary to Applicants arguments, if the Queen reference taught all the limitations of the instant claims, this rejection would be a 35 USC 102(b) rejection rather than a 35 USC 103 rejection. The Queen reference is cited in the instant rejection because it teaches administering humanized antibodies to IL-6R. Queen et al., (column 13, lines 5-65) teaches the humanization of monoclonal antibodies, as well as the issues involved in designing a humanized antibody that retains high affinity for its antigen and therefore teaches chimeric and humanized IL-6 receptor antibodies which the '510 reference does not disclose.

Applicants also argue that both Burstein and Queen, therefore, fail to teach that an antibody binding to an IL-6 receptor, as administered to a patient, would treat inflammatory bowel disease, neither reference fairly suggests that the teachings of either reference can be extended to encompass the claimed antibody binding to an IL-6 receptor and hence, one skilled in the art reading Queen and Burstein, either singly or in combination, would not find the claimed method obvious. However, contrary to Applicants arguments, as argued by the Examiner in paragraph 6a above, since claim 43 recites the term "comprising", this language

encompasses treating inflammatory diseases such as inflammatory bowel diseases by blocking a signal via the other receptors i.e. leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M and cardiotrophin-1 receptors. Therefore, reference '481 in view of Queen '101 renders obvious claims 43-47.

Non-statutory double patenting rejection (obviousness-type)

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8a. Claims 43-47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,723,319 ('319).

Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 43-47 in the instant application claim a method of treating inflammatory bowel disease, said method comprising administering to a subject in need thereof an anti-interleukin-6 receptor antibody which binds to interleukin-6 receptor, blocks signal transduction by IL-6 and inhibits the biological activity of IL-6. Claims 1-4 of U.S. Patent No. '319 (having all three common inventors with the instant application), claims a method of treating inflammatory bowel disease, said method comprising administering an anti-interleukin-6 receptor antibody, wherein the antibody used is the monoclonal antibody, PM-1 or MR16-1, against human IL-6 receptor. It is clear that the claims differ in scope because claims 1-4 of the '319 patent recites a method of treating inflammatory bowel disease by administering specific monoclonal antibodies but not the generic anti-IL-6 receptor antibody recited in instant claims 43-47. Instant claims 43-47 are genus claims to claims 1-4 in the patent. The patented claims are obvious from the instant claims because the patented claims are directed to specific embodiments encompassed by the instant claims. The patented method is included in the method of the instant claims.

It would have been obvious to one of ordinary skill in the art at the time the present invention was made, that a method of treating inflammatory bowel disease, said method comprising administering to a subject in need thereof an anti-interleukin-6 receptor antibody which binds to interleukin-6 receptor, blocks signal transduction by IL-6 and inhibits the biological activity of IL-6 included a method of treating inflammatory bowel disease, said method comprising administering an anti-interleukin-6 receptor antibody, wherein the antibody used is the monoclonal antibody, PM-1 or MR16-1, against human IL-6 receptor. The patented

claims if infringed upon would also result in infringement of the broad claims of the instant application. Allowance of the pending claims, therefore, would have the effect of extending the enforceable life of the allowed claims beyond the statutory limit.

Conclusion

No claim is allowed.

Claims 43-47 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Prema Mertz/
Primary Examiner
Art Unit 1646